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|---|-------------|----------------------|---------------------|------------------|
| 10/775,964  | 02/10/2004  | Jia-Hwa Fang         | PP16502.015         | 1609             |
| 7590 04/04/2008   |             |                      |                     |                  |
| Alisa Harbin, Esq.<br>Novartis Vaccines and Diagnostics, Inc.<br>Intellectual Property - R440<br>P. O. Box 8097<br>Emeryville, CA 94662 |             |                      |                     |                  |
| EXAMINER  |             |                      |                     |                  |
| FUBARA, BLESSING M  |             |                      |                     |                  |
| ART UNIT  |             | PAPER NUMBER         |                     |                  |
| 1618  |             |                      |                     |                  |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/775,964

**Applicant(s)**

FANG ET AL.

**Examiner**

BLESSING M. FUBARA

**Art Unit**

1618

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 14 January 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 34-42 and 62-76 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 34-42 and 62-76 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB06)  
Paper No(s)/Mail Date 1/14/2008
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

The examiner acknowledges receipt of request for extension of time, request for continued examination filed under 37 CFR 1.114, amendment and remarks, all filed 1/14/08. New claims 71-76 are added. Claims 34 and 39 are amended. Claims 43, 44 and 58-61 are canceled. Claims 34-42 and 62-76 are pending.

#### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/14/2008 has been entered.

#### ***Response to Arguments***

**Previous rejections that are not reiterated herein are withdrawn.**

#### ***Claim Rejections - 35 USC § 102***

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3. Claims 34-42 and 62-76 are rejected under 35 U.S.C. 102(a) as being anticipated by O'Hagan et al. (WO 00/50006).

O'Hagan discloses method of preparing microparticles by forming microemulsion by combining an organic solvent and polymer that is selected from the group consisting of poly( $\alpha$ -

hydroxy acid), a polyhydroxy butyric acid, polycaprolactone, polyorthoester, polyanhydride and polycyanoacrylate and anionic or cationic detergent, removing the organic solvent and recovering the microparticles (page 7, last full paragraph, pages 8-11) by filtration (Example 2). The % amount of detergent that in the microparticles in claims 34, 37, 39 and 62-68. Macromolecules such as polynucleotides and polypeptides are adsorbed onto the particles (page 2, 4<sup>th</sup> full paragraph) meeting claims 34, 37, 39 and 72-76. The CTAB used (Tables 19A and 19B) meets claims 38 and 40.

***Claim Rejections - 35 USC § 103***

4. Claims 34-42 and 62-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. (US 6,395,253) in view of Paliard et al. (US 6,562,346). New claims 68-70 are included in the rejection.

LEVY discloses preparation of microspheres that contain DNA or RNA as the bioactive agent (column 4, lines 31, 54 and 55). LEVY prepares a double emulsion of water-in-oil-in-water emulsion by using a condensing agent in one phase and the method comprises the steps of: "(a) dissolving at least one polymer in a water-immiscible organic solvent to yield an organic phase; (b) dissolving a polyanionic bioactive agent in aqueous solution to yield a first aqueous phase; (c) emulsifying the organic and first aqueous phases to yield a first milky emulsion; (d) dissolving a condensing agent in aqueous solution to yield a second aqueous phase; (e) emulsifying the first milky emulsion and the second aqueous phase to yield a second milky emulsion; and (f) removing the organic solvent from the second milky emulsion to yield microspheres containing condensed polyanionic bioactive agent with the emulsion meeting claims 34, 35 and 36-39. "The removal of the organic solvent in the final step is preferably by

Art Unit: 1618

means of evaporation," in one illustrative embodiment (column 4, lines 44 and 45). DNA and RNA are macromolecules and are polynucleotides meeting the requirements of claims 74-76. The concept of microspheres meets the microparticle limitation of claims 34, 37, 39, 42, 62, 65-70. Regarding the recitation that the microparticles are not subjected to washing step, it is noted that while the examples in Levy disclose a wash step, the basic preparation disclosed by Levy in section 4.2 does not state a wash step but rather that the microspheres are collected by ultracentrifugation and the alternative protocol disclosed in 4.6 and the comprising language is open. Levy uses 0.1% detergent (SDS in this case). There is no demonstration in applicants' specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles. The claims do not recite amount of detergent added to make the microparticle in the emulsion.

Regarding claim 36, which is directed to the process of cross-flow filtration, it is noted that in the cross-flow filtration process of the examined application, four liters of deionized water (Example 5) is used to remove the detergents and this appears to be equivalent to washing so that the cross-filtration step of the claim 34 reads on optional wash step of one of embodiments of Levy at column 13, line 5; at column 18, line 42 (washed with tris-EDTA); at column 20, line 2 (cells washed with PBS buffer). There is also no demonstration that the cross-filtration step performed after removing the organic solvent provides unusual results; Levy discloses filtration as one of the steps. The filtration step in Levy meets the filtration step in claims 34 and 37.

Regarding the ratio of lactide to glycolide, it is noted that there is no demonstration by applicants that the recited ratio provides unusual/unexpected results. The silence of Levy on the ratio of lactide to glycolide is an indication that the lactide/glycolide can be used in any desired

ratio that would be effective as a condensing agent for the DNA or RNA macromolecules. Levy also teaches polypeptide (column 4, line 64) meeting claim 72 and the SDS meets claim 71.

Regarding new claims 68-70, Levy in one of the embodiments does not wash the product but removes the solvent from the emulsion by evaporation so that the detergent is not removed or washed off (column 12, lines 58-67).

Levy uses SDS detergent. While Levy does not specifically state the presence of bound detergent in the amounts recited in the claims, it is noted that Levy does not specifically state that the microspheres/particles formed are free of detergent; and it flows from one of the embodiment that does not use a wash step but evaporates off the organic solvent (column 12, lines 58-67) that the detergent is not removed and as such, the microparticles would have detergent associated. However, while Levy teaches SDS and TWEEN, Levy does not disclose the use of cetyl trimethyl ammonium bromide (CTAB) detergent. But Paliard discloses an emulsion that comprises PLG polymer and CTAB (Example 5). Thus Paliard is relied upon for a teaching that the specific CTAB detergent can be used with PLG in an emulsion. CTAB and the SDS meet the detergent limitations of claims 38, 40, 68, 71. Therefore, taking the teachings of the references together, one having ordinary skill in the art at the time at the invention was made would have reasonable expectation of success that including the detergent CTAB in the double emulsion of Levy would produce emulsion whose particles would effectively adsorb polynucleotides and polypeptides that would be expected to release/deliver the polynucleotide and the polypeptide as desired.

***Response to Arguments***

5. Applicant's arguments filed 1/14/08 have been fully considered but they are not persuasive.

Applicant argues a) that applicant requires the absence of wash step, that Levy does not disclose the amounts of bound and unbound detergent claimed and "absent a reason to ensure that unbound detergent remains in the microparticles, one of ordinary art would be motivated to wash the microparticles of excess detergent by centrifugation." The PTO does not have laboratory facility to provide the factual evidence and at the same time the applicant has not provided factual evidence that the particles of Levy contains less than the amount of the detergent claimed. It is also noted Levy does not say to wash the particles to remove excess detergent. Furthermore, the examiner agrees with applicant that Levy does not disclose amount of bound or unbound detergent and it was for that reason that a rejection under 35 USC was not made. Rather, Levy does not categorically state that the microspheres produced are free of detergents and furthermore, Levy in one of the embodiments (column 12, lines 58-67) does not employ a wash step. It is also noted that instant claim 36 uses a cross-flow filtration step in which as gleaned from the specification at Example 5, four liters of deionized water is used to remove detergents.

b) that the examiner has not met the burden regarding the amount of the detergent bound and unbound, with respect to bound and unbound detergent amount, it is noted that the amount of detergent on the microparticles is inherent and it is within the technical skills of the artisan to determine how much detergent is associated with the particles and applicant has not provided any factual evidence that the microparticles do not have associated detergents.

c) that the washing step of Levy is not a filtration step and cross-flow filtration is not equivalent to washing; it is noted as was described previously in the Office action of 05/04/07, that Hawley's Condensed Chemical Dictionary, 14<sup>th</sup> edn., however filtration that collects particles or solids accomplishes the collection of particles or solid by centrifugation and the removal of unwanted components soluble and present in the solvent. The Hawley's condensed dictionary cited by applicant describes filtration as separation of suspended solids from liquids.

d) that in Levy, the use of the SDS occurred after the formation of DNA containing microspheres, but selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results.

e) that Paliard does not cure the deficiency of Levy, but it is noted that Paliard is relied upon for teaching the use of CTAB with PLGA polymer.

Applicant appears to be arguing against the individual references by addressing the references separately and one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

6. Claims 34, 35, 36 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hagan et al. (US 6,086,901).

O'Hagan discloses the process of preparing an emulsion that comprises poly(lactide-glycolide), solvent and detergent (Example 1); O'Hagan discloses that the size of the droplets (particle, microsphere) depends on the ratio of the detergent to oil (column 12, lines 38-47) and



also that water-in-oil-water (w/o/w) type emulsion can be formed of the microparticle (column 10, lines 9-20). The process of claim 36 reads on washing because in the cross-flow filtration process, 4 liters of deionized water (Example 5) are used and the removal of the water appears to approximate the process of filtration/washing. Emulsion and particles meet the emulsion and particle requirements of claims 34, 35 and 43. Claim 42 is a product by process claim and O'Hagan's particles meet the claim. While O'Hagan discloses a washing step, there is no demonstration in applicants' specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles. Therefore, taking the teaching of the prior art, one having ordinary skill in the art at the time the invention was made would have reasonable expectation of success to prepare biodegradable microparticles for administration to vertebrates to effect immunization.

***Response to Arguments***

7. Applicant's arguments filed 1/14/08 have been fully considered but they are not persuasive.

Applicant argues that O'Hagan teaches a wash step and cannot therefore render obvious the claimed method, but, the claims recite broad category of filtration which applicant argues results in unbound and bound detergent. Thus if a generic filtration process provides bound or unbound detergent, it flows that the O'Hagan's filtration of composition containing particles and detergent would also provide unbound and bound detergent. Furthermore, the comprising language of the claims is open permitting the presence of other steps and selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results.

No claim is allowed.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Blessing M. Fubara/  
Examiner, Art Unit 1618